FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
219217US0PCT	10/049904

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/05521	18 AUGUST 2000	23 AUGUST 1999 (EARLIEST)

TITLE OF INVENTION

SUBSTITUTED BENZYLTHIAZOLIDINE-2, 4-DIONE DERIVATIVES

APPLICANT(S) FOR DO/EO/US

Hiroyuki MIYACHI, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

    Notice of Priority / PTO-1449

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/049904	PCT/JP00/05521	219217US0PCT

IC10 Rec'd PCT/PTO 20 FEB 2002

24. The following fees are submitted:.		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :			
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1040.00**		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$890.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$740.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$710.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	10 - 20 =	0	x $18.00	**$0.00**	
Independent claims	4 - 3 =	1	x $84.00	**$84.00**	
Multiple Dependent Claims **(check if applicable).**			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$974.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$0.00**	
SUBTOTAL =				**$974.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
TOTAL NATIONAL FEE =				**$974.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
TOTAL FEES ENCLOSED =				**$974.00**	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of **$974.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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NAME

24,618
REGISTRATION NUMBER

Feb. 20 2002
DATE

SPECIFICATION

Title of the invention

Substituted benzylthiazolidine-2,4-dione derivatives

Technical field

The present invention relates to substituted benzylthiazolidine-2,4-dione derivatives effective for the prevention and/or therapy of metabolic diseases such as diabetes and hyperlipidemia as agonists of peroxisome proliferator-activated receptor (abbreviated as PPAR) being nuclear receptor, in particular, as agonists of human PPAR, their addition salts, process for preparing them, and medicinal compositions containing these compounds.

Background technologies

The peroxisome proliferator-activated receptor(PPAR) is a ligand-dependent transcription factor that belongs to nuclear receptor superfamily similarly to steroid receptor, retinoid receptor, thyroid receptor, etc., and three isoforms (α type, β(or δ) type and γ type) with different histological distribution have been identified hitherto in human and various animal species (Proc. Natl. Acad. Sci., 1992, 89, 4653). Thereamong, the PPARα is distributed in the liver, kidney, etc. with high catabolic capacity for fatty acids and, particularly high expression is recognized in the liver, (Endo-crinology, 1995, 137, 354), positively or negatively controlling the expression of genes related to the metabolism and the intracellular transport of fatty acids (e.g. acyl CoA synthetic enzyme, fatty acid-binding protein and lipoprotein lipase) and apolipoprotein (AI, AII, CIII) genes related to the metabolisms of cholesterol and triglycerides. The PPARβ is expressed ubiquitously in the tissues of organisms including

around nerve cells. At present, the physiological significance of PPARβ is unclear. The PPARγ is highly expressed in the adipocytes and contributed to the differentiation of adipocytes (J. Lipid Res., 1996, 37, 907). In this way, each isoform of PPAR play specific functions in the particular organs and tissues.

Moreover, it is reported that a knock-out mouse of PPARα exhibits hypertriglyceridemia with ageing and becomes obesity mainly by increasing the white adipocytes (J. Biol. Chem., 1998, 273, 29577), hence the relevance between activation of PPARα and decreasing action of lipids (cholesterol and triglyceride) in blood is suggested strongly.

On the other hand, fibrates and statins are widely used so far as the therapeutic drugs for hyperlipidemia. However, the fibrate type drugs have only weak decreasing action of cholesterol, while the statin type drugs have weak decreasing action of free fatty acids and triglycerides. Moreover, with respect to the fibrate type drugs, various adverse effects such as gastrointestinal injury, anthema, headache, hepatic disorder, renal disorder and biliary calculus are reported. The reason is considered to be due to that the fibrate type drugs exhibit extensive pharmacological function.

On the other hand, it is ascertained that the major intracellular target protein of Troglitazone, Pioglitazone and Rosiglytazone being a series of thiazolidine-2,4-dione derivatives that are therapeutic drugs for type II diabetes (noninsulindependent diabetes) and exhibit blood glucose-decreasing action, improving action on hyperinsulinemia, etc. are PPARγ, and these drugs increase the transactivation of PPARγ (Endocrinology, 1996, 137, 4189, Cell., 1995, 83, 803, Cell., 1995, 83, 813). Hence, PPARγ-activator (agonist) that

increases the transactivation of PPARγ is important as antidiabetic drug.

As described, when considering the roles of transcription factor called PPAR on the function on adipocytes and the controlling mechanisms of glucose metabolism and lipid metabolism, if a compound that binds directly to as a ligand of PPAR, in particular, human PPAR and can activate human PPAR could be created, it would be reasonable to expect the medicinal use as a compound that exhibits blood glucose-decreasing action and/or decreasing action of lipids (both of cholesterol and triglyceride) in blood due to very specific mechanism.

For compounds having an affinity to PPARα as ligands of PPARα, HEPE (hydroxyeicosapentaenoic acid) produced via oxidation with cytochrome P-450 and eicosanoides in HETE (hydroxyeicosatetraenoic acid) groups, in particular, 8-HETE, 8-HEPE, etc. are reported in addition to LTB_4, being a metabolite of arachidonic acid (Proc. Natl. Acad. Sci., 1997, 94, 312). However, these endogenous unsaturated fatty acid derivatives are unstable metabolically and chemically and cannot be offered as medicinal drugs.

Moreover, with Troglitazone, the occurrence of serious adverse effect on liver is reported rarely, hence the development of a therapeutic drug for type II diabetes with effectiveness and high safety is being sought.

Now, as compounds with similar structure to the inventive substituted benzylthiazolidine-2,4-dione derivatives, thiazolidine-2,4-dione derivatives in Japanese Unexamined Patent Publication Nos. Sho 55-22636, Sho 60-51189, Sho 61-85372, Sho 61-286376, Hei 1-131169, Hei 2-83384, Hei 5-213913, Hei 8-333355, Hei 9-48771 and Hei 9-169746, European

Patent Open No. 0441605, WO-92/07839, etc. are known. However, all of these compounds are thiazolidine-2,4-dione derivatives with different structure from the inventive compounds.

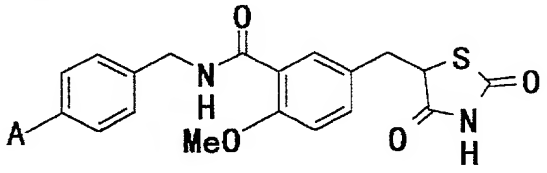
With regard to patents etc. reporting the agonistic effect on PPAR α, WO-97/25042, WO-97/36579, etc. are reported, but all of these have different structure from the inventive compounds and the transactivation function of PPARα is also never satisfied in strength.

Both the hyperlipidemia and the diabetes are risk factors of arterosclerosis and, from a viewpoint of the prevention of arterosclerosis, in particular, coronary arterosclerosis, the development of a therapeutic drug for metabolic diseases with effectiveness and high safety is desired clinically.

Disclosure of the invention

As a result of diligent studies paying an attention to such specific roles on the lipid metabolism of human PPAR, differentiation of adipocytes, etc. aiming at the creation of structurally novel drug with effectiveness and high safety as a therapeutic drug for metabolic diseases, the inventors have found that novel substituted benzylthiazolidine-2,4-dione derivatives represented by the following general formula (1) have excellent transactivation function of human PPAR, and exhibit the blood glucose-decreasing action and the lipid-decreasing action, leading to the completion of the invention.

Namely, the invention relates to substituted benzylthiazolidine-2,4-dione derivatives represented by the general formula (1)



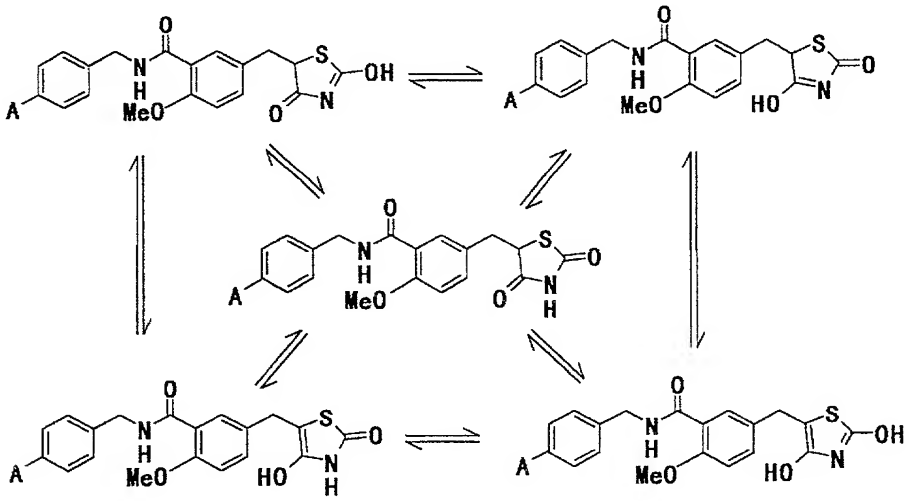
(1)

[wherein A denotes a phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is unsubstituted or may have substituents], their medicinally acceptable salts and their hydrates.

The salts of the compounds represented by the general formula (1) in the invention are of common use and metal salts, for example, alkali metal salts (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g. calcium salt, magnesium salt, etc.), aluminum salt, and other pharmacologically acceptable salts are mentioned.

Moreover, the compounds represented by the general formula (1) in the invention sometimes include optical isomers based on thiazolidine-2,4-dione ring portion, but all of such isomers and their mixtures are to be included in the scope of the invention.

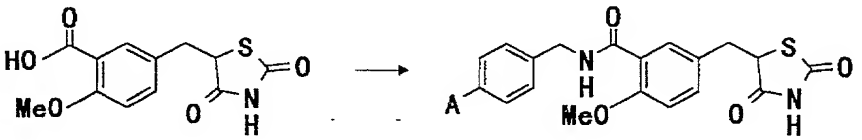
Furthermore, for the compounds represented by the general formula (1), the existence of various tautomers is considered. These are, for example, as shown in the following formulae.



[wherein A denotes a phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is unsubstituted or may have substituents]. In the general formula (1) aforementioned, all of these isomers and their mixtures are to be included in the scope of this invention.

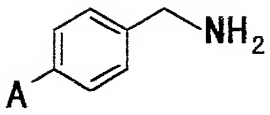
In the general formula (1) of the invention, for the substituents permissible in "phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is unsubstituted or may have substituents", lower alkyl group with carbon atoms of 1 to 4, lower alkoxy group with carbon atoms of 1 to 3 and halogen atom are mentioned.

According to the invention, the compounds being said the general formula (1) can be prepared, for example, through the following process (Scheme 1).



Scheme 1

Namely, the compounds represented by the general formula (1) can be prepared by reacting (first process) publicly known (Japanese Unexamined Patent Publication No. Hei 8-333355) compound (2) and the compounds represented by the general formula (3)



(3)

[wherein A denotes a phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is unsubstituted or may have substituents].

The first process can be performed by leaving the carboxyl group as it is, or converting it to the reactive derivative.

As the "reactive derivative group of the carboxyl group", acid chloride, acid bromide, acid anhydride, carbonylimidazole or the like can be mentioned. In the case of the reaction using the reactive derivative, the reaction can be performed in a solvent such as methylene chloride, chloroform, dioxane or N,N-dimethylformamide in the presence or absence of, for example, alkali metal hydride such as sodium hydride, alkali metal hydroxide such as sodium hydroxide, alkali metal carbonate such as potassium carbonate, or organic base such as pyridine or triethylamine as a base.

In the case of conducting the reaction by leaving the carboxylic acid as it is, the reaction can be performed in a solvent such as methylene chloride, chloroform, dioxane or N,N-dimethylformamide in the presence of condensing agent in the presence or absence of base, in the presence or absence of additive.

As the condensing agent, for example, dicyclohexylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, diethyl cyanophosphate,

diphenylphosphoric azide, carbonyldiimidazole or the like can be mentioned. As the base, for example, alkali metal hydroxide such as sodium hydroxide, alkali metal carbonate such as potassium carbonate, or organic base such as pyridine or triethylamine can be mentioned. As the additive, N-hydroxybenzotriazole, N-hydroxysuccinimide, 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine or the like can be mentioned. The reaction can be performed at a reaction temperature of -20°C to 100°C, preferably at 0°C to 50°C.

As the administering form of the novel compounds of the invention, for example, oral administration with tablet, capsule, granule, powder, inhalant, syrup or the like, or parenteral administration with injection, suppository or the like can be mentioned.

Best embodiment to put the invention into practice

In following, the invention will be illustrated based on concrete examples, but the invention is not confined to these examples.

(Example 1)

N-[(4-Benzyloxyphenyl)methyl]-5-[(2,4-dioxothiazolidin-5-yl)-methyl]-2-methoxybenzamide

5-[(2,4-Dioxothiazolidin-5-yl)methyl]-2-methoxybenzoic acid (422mg, 1.50mmol), triethylamine (0.523mL, 3.75mmol) and methylene chloride (5mL) were mixed and ethyl chlorocarbonate (0.158mL, 1.50 mmol) was added under cooling with ice and stirring. After stirring for 10 minutes under cooling with ice, a solution of 4-(benzyloxy)benzylamine (319mg, 1.50mmol) dissolved in methylene chloride (2mL) was added. The mixture was stirred for 2 hours at room temperature, and then allowed to stand overnight. After washed with water, the reaction mixture was dried over anhydrous sodium sulfate and

concentrated. The residue was dissolved in water (40mL), which was made acidic with 10% hydrochloric acid and stirred for 30 minutes. The precipitated crystals were collected by filtration, dried, and then recrystallized from a mixed solution of ethanol and water to obtain 549mg (77%) of the title compound as colorless powder.

Melting point 131.0-132.5°C;

Mass analysis m/z 476(M^+);

Elemental analysis(%) $C_{26}H_{24}N_2O_5S$:

Calcd.(%) C, 65.53; H, 5.08; N, 5.88.

Found (%) C, 65.68; H, 5.08; N, 5.91.

(Examples 2 and 3)

Similarly to Example 1, the following compounds were obtained.

(Example 2)

N-[(Biphenyl-4-yl)methyl]-5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-methoxybenzamide

Melting point 170.5-172.0°C;

Mass analysis m/z 446(M^+);

Elemental analysis(%) $C_{25}H_{22}N_2O_4S$:

Calcd.(%) C, 67.25; H, 4.97; N, 6.27.

Found (%) C, 67.29; H, 4.99; N, 6.21.

(Example 3)

N-[(4-Phenoxyphenyl)methyl]-5-[(2,4-dioxothiazolidin-5-yl)meth-yl]-2-methoxybenzamide

Melting point 87.0-89.0°C;

Mass analysis m/z 462(M^+);

Elemental analysis(%) $C_{25}H_{22}N_2O_5S \cdot 1/5H_2O$:

Example	A	Melting point (°C)	Mass analysis (m/z)	Charac. formula	Elemental analysis (%)
4	4-OPh(2-OMe)	Amorphous	492(M^+)	$C_{26}H_{24}N_2O_6S$	Cald.; C63.40,H4.91,N5.69 Found; C63.05,H4.95,N5.57
5	4-OPh(3-OMe)	Amorphous	492(M^+)	$C_{26}H_{24}N_2O_6S$	Cald.; C63.40,H4.91,N5.69 Found; C63.13,H4.95,N5.54
6	4-OPh(4-OMe)	Amorphous	492(M^+)	$C_{26}H_{24}N_2O_6S$	Cald.; C63.40,H4.91,N5.69 Found; C63.05,H4.99,N5.54
7	4-OPh(3-Me)	154.0-156.0	476(M^+)	$C_{26}H_{24}N_2O_5S$	Cald.; C65.53,H5.08,N5.88 Found; C65.29,H5.16,N5.79
8	4-OPh(4-Me)	146.0-147.0	476(M^+)	$C_{26}H_{24}N_2O_5S$	Cald.; C65.53,H5.08,N5.88 Found; C65.20,H5.10,N5.87
9	4-Ph(4-Cl)	200.0-202.0	480(M^+)	$C_{25}H_{21}ClN_2O_4S \cdot 1/4H_2O$	Cald.; C61.85,H4.46,N5.77 Found; C61.92,H4.35,N5.74
10	4-Ph(4-OMe)	201.0-202.0	476(M^+)	$C_{26}H_{24}N_2O_5S \cdot 1/4H_2O$	Cald.; C64.92,H5.13,N5.82 Found; C65.02,H5.12,N5.81
11	4-OCH_2Ph(4-Cl)	158.0-160.0	510(M^+)	$C_{26}H_{23}ClN_2O_5S$	Cald.; C61.11,H4.54,N5.48 Found; C61.22,H4.53,N5.46
12	4-OCH_2Ph(4-Me)	181.0-183.0	490(M^+)	$C_{27}H_{26}N_2O_5S \cdot 1/4H_2O$	Cald.; C65.50,H5.39,N5.66 Found; C65.37,H5.28,N5.57
13	4-Ph(4-Me)	190.0-192.0	460(M^+)	$C_{26}H_{24}N_2O_4S$	Cald.; C67.81,H5.25,N6.08 Found; C67.56,H5.22,N6.02

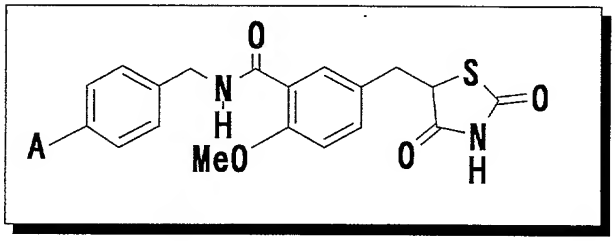
Calcd.(%) C, 64.42; H, 4.84; N, 6.01.

Found (%) C, 64.17; H, 4.81; N, 6.03.

(Examples 4 through 13)

Similarly to Example 1, the compounds in Table 1 were obtained.

(Table 1)



<Biological activity>

(Test example 1)

Test of transactivation on peroxisome proliferator-activated receptors α and γ

To CHO cells cultured in a Ham's F-12 medium containing fatty acid free 10% fetal calf serum, receptor plasmid and its reporter plasmid (STRATAGENE Corp.) that express fused protein of DNA-binding domain being transcription factor of yeast with ligand-binding domain of human type PPARs α and γ (Biochemistry, 1993, 32, 5598), and β-galactosidase plasmid (Promega Corp.) for internal standard were cotransfected with lipofectamine in the serum-free state. Thereafter, testing compound and control compound (Troglitazone or Pioglitazone for control drug of PPAR γ, and (8S)-HETE for control drug of PPAR α) were dissolved into DMSO and adjusted with Ham's F-12 medium containing fatty acid free 10% fetal calf serum, so that the final concentration of DMSO became 0.01% to culture. After 24 hours, CAT activity and β-galactosidase activity were measured.

Results are shown in Table 2. From these results, it was shown that the inventive compounds had potent transactivation action on human peroxisome proliferator-activated receptors α and γ.

(Table 2)

Transactivation action

Example	PPARα	PPARγ
	EC_{50}(μmol/L)	EC_{50}(μmol/L)
1	0.44	—
2	0.63	6.8
3	0.24	0.24
Troglitazone	—	1.15
Pioglitazone	—	0.72
(8S)-HETE	1.3	—

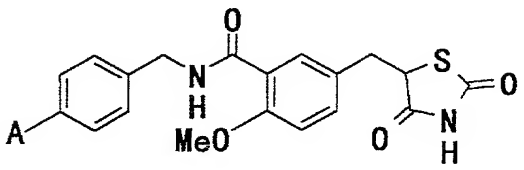
Utilizability in the industry

From the results as descried above, the inventive substituted benzylthiazolidine-2,4-dione derivatives are novel compounds group with excellent human PPAR transactivation.

From the fact that these inventive compounds have agonistic activity on human PPAR, it can be said that they are effective compounds as blood glucose-decreasing drugs and therapeutic drugs for hyperlipidemia aforementioned.

SCOPE OF THE CLAIM

1. Substituted benzylthiazolidine-2,4-dione derivatives represented by a general formula (1)



(1)

[wherein A denotes a phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is unsubstituted or may have substituents], their medicinally acceptable salts and their hydrates.

2. The substituted benzylthiazolidine-2,4-dione derivatives, their medicinally acceptable salts and their hydrates of Claim 1, wherein A is phenyl group which is unsubstituted or may have substituents.

3. The substituted benzylthiazolidine-2,4-dione derivatives, their medicinally acceptable salts and their hydrates of Claim 1, wherein A is phenoxy group which is unsubstituted or may have substituents.

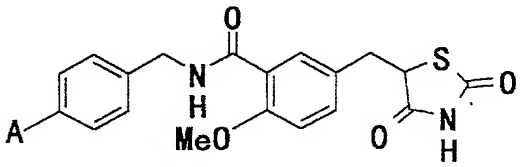
4. The substituted benzylthiazolidine-2,4-dione derivatives, their medicinally acceptable salts and their hydrates of Claim 1, wherein A is benzyloxy group which is unsubstituted or may have substituents.

5. A compound of Claim 1, being N-[(4-benzyloxyphenyl)-methyl]-5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-methoxybenzamide, its medicinally acceptable salts and its hydrates.

6. A compound of Claim 1, being N-[(4-phenoxyphenyl)methyl]-5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-methoxybenzamide, its medicinally acceptable salts and its hydrates.

7. A compound of Claim 1, being N-[(biphenyl-4-yl)methyl]-5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-methoxybenzamide, its medicinally acceptable salts and its hydrates.

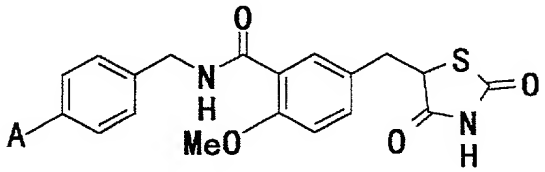
8. A blood glucose-decreasing drug having at least one or more kinds of substituted benzylthiazolidine-2,4-dione derivatives represented by the general formula (1)



(1)

[wherein A denotes a phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is unsubstituted or may have substituents], their medicinally acceptable salts and their hydrates as effective ingredients.

9. A lipid in blood-decreasing drug having at least one or more kinds of substituted benzylthiazolidine-2,4-dione derivatives represented by the general formula (1)

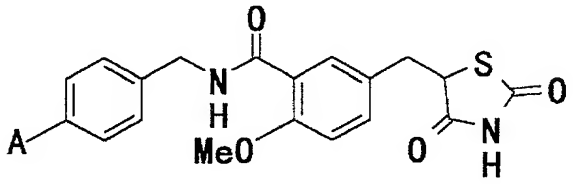


(1)

[wherein A denotes a phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is

unsubstituted or may have substituents], their medicinally acceptable salts and their hydrates as effective ingredients.

10. An agonistic drug of human peroxisome proliferator-activated receptor having at least one or more kinds of substituted benzylthiazoli-dine-2,4-dione derivatives represented by the general formula (1)



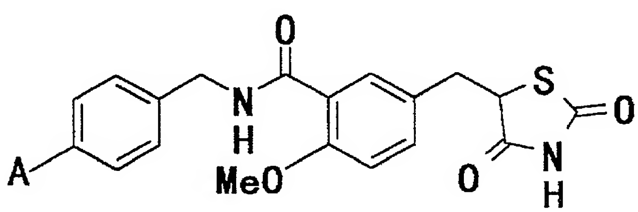
(1)

[wherein A denotes a phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is unsubstituted or may have substituents], their medicinally acceptable salts and their hydrates as effective ingredients.

SUMMARY

The invention provides novel substituted benzylthiazolidine-2,4-dione derivatives which increase the transactivation action of receptor as a ligand of human peroxisome proliferator-activated receptor (PPAR) and exhibit the blood glucose-decreasing action and lipid-decreasing action, and a process for preparing them.

The invention relates to substituted benzylthiazolidine-2,4-dione derivatives represented by the general formula (1)



(1)

[wherein A denotes a phenyl group which is unsubstituted or may have substituents, phenoxy group which is unsubstituted or may have substituents or benzyloxy group which is unsubstituted or may have substituents], their medicinally acceptable salts, their hydrates and a process for preparing them.

RP-9446 PCT

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Substituted benzylthiazolidine-2,4-dione derivatives

the specification of which

☒ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____.

☒ was filed as PCT international application

Number PCT/JP00/05521

on August 18, 2000,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
Hei 11-235529	Japan	23/08/1999	☒ Yes ☐ No
2000/242707	Japan	10/08/2000	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. 30,996; Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Martin M. Zoltick, Reg. No. 35,745; Robert W. Hahl, Reg. No. 33,893; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; and Paul E. Rauch, Reg. No. 38,591; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and ~~to transact~~ all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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